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L3: Entry 47 of 85 File: PGPB Apr 24, 2003

DOCUMENT-IDENTIFIER: US 20030078210 A1
TITLE: Compounds and methods for modulating cell-adhesion mediated drug resistance

Summary of Invention Paragraph:
[0001] The present invention relates to the use of pharmaceutical agents to modulate cell-adhesion. In particular, the invention relates to the use of peptides for inhibiting cell-adhesion and enhancing the efficacy of chemotherapeutic and/or radiation treatments in the treatment of cancer.

Summary of Invention Paragraph:
[0017] It is a further aspect of the present invention to provide a protocol comprising the administration of pharmaceutical agents that disrupt cancer cell adhesion in vivo to enhance the efficacy of chemotherapeutic and/or radiation treatments.

Summary of Invention Paragraph:
[0018] It is a further aspect of the present invention to provide a protocol comprising the administration of peptides for inhibiting adhesion and thereby enhancing the efficacy of chemotherapeutic and/or radiation treatments in the treatment of cancer.

Detail Description Paragraph:
[0144] In summary, integrin-mediated FN adhesion is shown to cause a decreased response to chemotherapeutic drugs as well as a correlation between the expression of .alpha..sub.4 integrin heterodimers and drug resistance. The term cell adhesion mediated drug resistance, or CAM-DR, describes this observation. Two well established causes of drug resistance, active drug transport and increased expression of Bcl-2 family members, are shown not to produce these effects. Clinically, elevated FN receptor expression or function in myeloma cells within the bone marrow may be an indicator of a more aggressive tumor cell which has a survival advantage against the cytotoxic effects of anti-cancer drugs. In vivo alterations in fibronectin receptor expression or function may have a magnified effect on myeloma cell survival when they are in direct association with stromal cells and ECM components of the bone marrow. The cytoprotection conferred by fibronectin receptors may be low level, but intrinsic, since most myeloma cells inherently express moderate to high levels of these integrins. Small changes in drug sensitivity in vitro are probably highly relevant clinically since even a 1 percent surviving tumor fraction can have drastic long term consequences. The CAM-DR mediated by FN adhesion may be sufficient to allow the eventual emergence of drug resistance mechanisms such as upregulation of P-glycoprotein, MRP, and alterations in topoisomerase II, which then become the predominant cytoprotective processes. Therefore, specific integrin subunits and the various signal transduction elements they utilize, provide promising therapeutic targets. Established antagonists of VLA-4 and VLA-5 integrin function may serve as chemosensitizers when administered in conjunction with conventional chemotherapeutics, leading to higher levels of drug response and improved clinical outcome.

Detail Description Paragraph:
[0204] It is also shown that specific agents including peptides such as the

synthetic D-amino acid peptide RZ-3 can be utilized to inhibit integrin-mediated cell adhesion thereby rendering cancer cells more sensitive to chemotherapeutic agents. Thus, integrin-mediated cell adhesion confers resistance to chemotherapeutic agents and represents a novel and specific target for the development of therapies that can interfere with or inhibit CAM-DR. Furthermore, inhibition of CAM-DR has the potential to enhance treatment responses by sensitizing cancer cells to both chemotherapy and radiation therapy.

Detail Description Paragraph:
[0205] In particular, the use of peptides (such as RZ-3) for inhibiting adhesion and enhancing the efficacy of chemotherapeutic and/or radiation treatments in the treatment of cancer is disclosed.

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L3: Entry 73 of 85 File: USPT Jan 2, 1996

DOCUMENT-IDENTIFIER: US 5480901 A
TITLE: Method for reducing unwanted cellular adhesions

Brief Summary Text (8):
It has been proposed to reduce the occurrence of adhesion formation resulting from chemotherapeutic treatments involving cisplatin and bleomycin by administering these chemotherapeutic agents in combination with a vinca alkaloid substance, such as vindesine. R. Molloy et al., Irish J. Med. Sci., 159 (6): 175-77 (1990). However, no technique is provided for site specific delivery of the proposed chemotherapeutic combination.

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Terms	Documents
(adhesion) adj10 (chemotherapeutic or $estrogen)	85

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L1	(adhesion) adj10 (chemotherapeutic or anti$ or $estrogen)	7706	L1

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